BL6

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 47/26, 35/66, 9/20 — A1

(11) International Publication Number: WO 97/07822

(43) International Publication Date: 6 March 1997 (06.03.97)

(21) International Application Number: PCT/SE96/01043

(22) International Filing Date: 23 August 1996 (23.08.96)

(30) Priority Data:
9502941-9 25 August 1995 (25.08.95) SE

(71) Applicant *(for all designated States except US)*: DETUM AB [SE/SE]; P.O. Box 531 82, S-400 15 Göteborg (SE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: CEDGÅRD, Lennart [SE/SE]; Skolgatan 26, S-413 02 Göteborg (SE).

(74) Agents: GRAUDUMS, Valdis et al.; Albihn West AB, P.O. Box 142, S-401 22 Göteborg (SE).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
With amended claims.
In English translation (filed in Swedish).

(54) Title: METHOD FOR THE PRODUCTION OF TABLETS BY PRESSING AND TABLETS PRODUCED BY THE METHOD

(57) Abstract

The invention relates to a method for the production of tablets by pressing of tablet material which comprises microorganisms. The method is characterized in that the tablet material also contains oligosaccharides, preferably inulin. The invention also includes tablets produced by the method according to the invention.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

TITLE: Method for the production of tablets by pressing and tablets produced by the method.

TECHNICAL FIELD:

The present invention relates to a method for the production of tablets by pressing of tablet material which contains microorganisms.

PRIOR ART:

Tablets are usually produced by pressing of a pulverulent tablet mass in a suitable shape in a so-called tablet punching machine. The tablets may have different shape and be of different size and they may also be of different hardness dependent on the properties of the tablet mass and the pressure to which they are subjected during the punching of the tablets.

When the tablets are formed heat is developed as a result of the friction against the mould surfaces and the inner friction in the tablet mass. Since the tablets usually consist of chemicals and the temperature increase is not too high, this will not create any problem since the chemicals can resist this heat increase and also are cooled rapidly. However, some tablet masses contain living microorganisms, such as bacteria, which are sensitive to high temperatures and because of this some of these bacteria die during the tablet punching.

TECHNICAL PROBLEM:

Tablets which contain microorganisms, for instance in the form of bacteria, and which are intended to contain such organisms will lose a part of or all of their value when the microorganisms are destroyed during the tablet punching. This cannot be avoided by simply using a lower pressure on the conventional tablet mass and thereby creating a lower heat development since the tablet must be

subjected to a certain pressure so that it maintains its shape and is not crumbled. For known tablet masses it is not unusual that a reduction of the viability (survival) of the bacteria in the tablet is up to 80% and even more.

SOLUTION:

It has therefore always been a problem to be able to produce tablets which contain microorganisms in the form of bacteria with a lesser reduction of the viability from tablet mass to a complete tablet and therefore according to the invention a method has been obtained for the production of tablets by pressing of tablet material comprising living organisms, which is characterized in that the tablet material also contains oligosaccharides consisting of more than two monosaccharides.

According to the invention, it is suitable that the oligosaccharides consist of fructose oligosaccharides, preferably inulin.

According to the invention it is suitable that the oligosaccharides are present in an amount of 40-99.5 % by weight of the tablet material.

The tablet material according to the invention can suitably contain microorganisms consisting of lactic acid producing bacteria.

The invention also comprises tablets produced by the method according to the invention, which tablets contain oligosaccharides and microorganisms whereby the oligosaccharides suitably consist of fructose oligosaccharides, preferably inulin.

The tablets according to the invention may contain lactic acid producing bacteria as microorganisms and they may also

contain other additives such as polysaccharides, for example microcrystalline cellulose and starch, as well as other additives such as calcium diphosphate.

DETAILED DESCRIPTION:

The tablets according to the invention comprise microorganisms, preferably lactic acid producing bacteria cultures known as probiotica, which are intended to normalise or balance bacterial flora being present in the stomach and the intestine of humans or animals, but they may also contain other types of bacteria.

By mixing oligosaccharides, preferably fructose oligosaccharides, in the tablet mass as a so-called supporting substance the tablet punching is facilitated, which makes it possible to punch tablets at a lower pressure and lower heat development at the same time as the hardness of the tablet is maintained. The brittleness of the tablet, the friability, is surprisingly not changed with the tablet mass according to the present invention.

Due to this new composition, the punching pressure for the tablet making maybe reduced by up to 50% compared to conventional tablet punching methods without any reduction of the friability. This friability according to the invention will be 0.3-0.5, which is to be compared with the reference values which are accepted according to GMP (Good Manufacturing Practice) which are within the range of 0.1-1.0. The friability is expressed in percent weight reduction of the tablets when they are rotated 100 revolutions in a standard testing machine.

The amount of oligosaccharides depends on different crystalline qualities but may suitably be 99.5-40 weight percent of the total tablet mass without admixing any other supporting substance. However, if desired, known supporting

substances such as calcium diphosphate, microcrystalline cellulose and starch may be added in a suitable small amount. A smaller addition of oligosaccharides can, however, give rise to a smaller difference with regard to the viability compared with tablet masses containing only conventional supporting substances.

The tablets according to the present invention have a lower hardness due to the lower punching pressure when the tablets are formed but an increased viability for the strain of bacteria, which makes every tablet more efficient than conventional tablets. By not pressing the tablets so hard the yield of tablets for a given amount of tablet mass will also increase.

The invention will be described more in detail below by means of two examples, of which Example 1 describes a method according to the present invention and Example 2 describes a method of conventional kind.

Example 1: recipe having an active substance and tablet filling material

Str. thermophilus & L. bulgaricus	50%
Bifidobacterium animalis	0.5%
L. plantaris	0.5%
Inulin (fructose oligosaccharides)	49%
	100%

Hardness: 2.75 kp Friability: 0.3
Viability original granulate: 5E8 cfu/g
Viability tablet: 3E8 cfu/g
40% reduction of cfu (colony forming units)

Example 2: recipe having active substance and tablet filling material

Str. thermophilus & L. bulgaricus	50%
Bifidobacterium animalis	0.5%
L. plantaris	0.5%
Calcium diphosphate	20%
Microcrystalline cellulose	18%
Starch	11%
	100%

Hardness: 5.5 kp Friability: 0.3%
Viability original granulate: 5E8 cfu/g
Viability tablet: 1E8 cfu/g
80% reduction of cfu (colony forming units)

As appears from the above examples, the friability is maintained unchanged with a value of 0.3 whereas the hardness has been decreased to 2.75 kp compared with 5.5 kp for the conventional method. The viability has increased from 1E8 cfu/g to 3E8 cfu/g according to the invention. The reduction of cfu from tablet mass to tablet during the tablet punching became only 40% according to the new method and 80% according to the conventional method.

Accordingly, the new method results in an increased maintained viability after tablet punching of up to 200% compared with conventional tablet fillers. The increased yield results in an appreciably better economy and quality improvement of the above products.

The invention is not limited to the embodiments shown above but can be varied in different ways within the scope of the claims.

CLAIMS:

1. Method for the production of tablets having high viability in the tablet by pressing tablet material containing living microorganisms, characterized in that the tablet material also contains oligosaccharides.

2. Method according to claim 1 characterized in that the oligosaccharides are present in an amount of 40-99.5 percent by weight of the tablet material.

3. Method according to any of claims 1-2, characterized in that the oligosaccharides consist of fructose oligosaccharides.

4. Method according to any of claims 1-3, characterized in that the oligosaccharides consist of inulin.

5. Method according to any of claims 1-4, characterized in that the microorganisms consist of lactic acid producing bacteria.

6. Tablets produced according to any of claims 1-5 containing oligosaccharides and microorganisms.

7. Tablets according to claim 6, characterized in that the oligosaccharides consist of fructose oligosaccharides.

8. Tablets according to any of claims 6-7, characterized in that the oligosaccharides consist of inulin.

9. Tablets according to any of claims 6-8, characterized in that the microorganisms consist of lactic acid producing bacteria.

10. Tablets according to any of claims 6-9, characterized in that they also contain polysaccharides such as microcrystalline cellulose and starch as well as other additives such as calcium diphosphate.

AMENDED CLAIMS

[received by the International Bureau on 24 December 1996 (24.12.96); original claims 1 - 10 replaced by amended claims 1 - 10 (2 pages)]

1. Method for the production of tablets having high viability in the tablet by pressing tablet material containing living microorganisms, c h a r a c t e r i z e d i n that the tablet material also contains oligosaccharides consisting of more than two monosaccharides.

2. Method according to claim 1 c h a r a c t e r i z e d i n that the oligosaccharides are present in an amount of 40-99.5 percent by weight of the tablet material.

3. Method according to any of claims 1-2, c h a r a c t e r i z e d i n that the oligosaccharides consist of fructose oligosaccharides.

4. Method according to any of claims 1-3, c h a r a c t e r i z e d i n that the oligosaccharides consist of inulin.

5. Method according to any of claims 1-4, c h a r a c t e r i z e d i n that the microorganisms consist of lactic acid producing bacteria.

6. Tablets produced according to any of claims 1-5 containing oligosaccharides and microorganisms.

7. Tablets according to claim 6, c h a r a c t e r i z e d i n that the oligosaccharides consist of fructose oligosaccharides.

8. Tablets according to any of claims 6-7, c h a r a c t e r i z e d i n that the oligosaccharides consist of inulin.

9. Tablets according to any of claims 6-8, c h a r a c t e r i z e d i n that the microorganisms consist of lactic acid producing bacteria.

10. Tablets according to any of claims 6-9, c h a r a c t e r i z e d i n that they also contain polysaccharides such as microcrystalline cellulose and starch as well as other additives such as calcium diphosphate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/01043

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 47/26, A61K 35/66, A61K 9/20
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, WPIL, CLAIMS, CAPLUS, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0227441 A1 (E.I. DU PONT DE NEMOURS AND COMPANY), 1 July 1987 (01.07.87), page 6, line 1 - line 11, claims ---	1-10
X	STN International, File CAPLUS, CAPLUS accession no. 1992:241966, Asahi Breweries, Ltd.: "Lactobacillus-containing tablets coated with intestinally soluble substances"; & JP,A2,04041434 920212 Heisei --- --------	1-10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 November 1996	29 -11- 1996
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/10/96

International application No.
PCT/SE 96/01043

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0227441	01/07/87	JP-A- 62168053	24/07/87